CORTICOSPINAL EXCITABILITY DURING SHORTENING AND LENGTHENING ACTIONS WITH INCREMENTAL TORQUE OUTPUT

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What is the central question of this study?

Relationship between motor unit recruitment and firing rate has been related to the size of the corticospinal output with variations in the nervous system gain during isometric contractions. However, corticospinal behaviour with incremental torque output might differ during anisometric contractions due to differences in neural control of anisometric contraction types.

What is the main finding and its importance?

Corticospinal excitability during lengthening contractions was smaller compared to shortening, but increased with incremental torque output similarly between contraction types. This suggests that the relationship between motor unit recruitment and firing rates is the likely main determinant of the size of an evoked response with variations in system gain.

ABSTRACT

The modulation of motor evoked potentials (MEPs), an index of corticospinal excitability, has been shown to increase during isometric contractions with incremental torque output in accordance with the contribution between motor unit recruitment and firing rate of the muscle to increases in required torque output. However, motor unit strategy of the muscle might not be the only factor influencing this behaviour since differences in pre- and postsynaptic control have been reported between lengthening and shortening or isometric contractions. In thirty healthy adults, MEPs were elicited in tibialis anterior during shortening and lengthening contractions at 15, 25, 50 and 80% contraction type specific maximal voluntary contraction torque. Background electromyographic activity increased progressively with greater torque output ($p<0.001$), but was similar between contraction types ($p=0.162$). When normalised to the maximal muscle response, MEPs were greater during shortening compared to lengthening

contractions ($p=0.004$) and increased step-wise with increased contraction intensities ($p=0.001$). These data show an increase in corticospinal excitability with torque output from lower to higher contraction intensities, suggesting greater contribution of motor unit recruitment to increased nervous system gain in the tibialis anterior. Despite differences in corticospinal control of shortening and lengthening contractions, the data suggest the corticospinal responses to increases in torque output are not dependent on contraction type since corticospinal excitability increased similarly during shortening and lengthening actions. Thus, it is likely that the relationship between motor unit recruitment and firing rate of the muscle is the main determinant of corticospinal output with variations in nervous system gain.

INTRODUCTION

The size of the motor evoked potentials (MEPs) when normalised to a maximal muscle response, an index of corticospinal excitability, is modulated by varying the nervous system gain. Data from isometric experimental models suggests that an increase in contraction strength or voluntary drive results in increased MEP size (peak to peak amplitude or area), sometimes followed by a decline, or plateau, at higher contraction strengths depending on the muscle (Goodall, Romer, & Ross, 2009; Martin, Gandevia, & Taylor, 2006; Todd, Taylor, & Gandevia, 2003; Weavil, Sidhu, Mangum, Richardson, & Amann, 2015). Specifically, muscles which rely on a greater degree of motor unit recruitment in response to an incremental force increase are likely to exhibit a peak in the evoked response at higher percentage of maximal contraction strength (Gelli, Del Santo, Popa, Mazzocchio, & Rossi, 2007; Martin et al., 2006). On the other hand, muscles that rely more on increases in motor unit firing rate for increases in force production are likely to exhibit a plateau or a decline in corticospinal excitability at lower percentages of maximal strength. This is due to the negative correlation between increases in motor unit firing rate and the probability of an evoked response (Bawa & Lemon, 1993; Brouwer, Ashby, & Midroni, 1989; Jones & Bawa, 1999). For example, the majority of arm and hand muscles (Todd *et al.*, 2003; Martin *et al.*, 2006) as well as the quadriceps (Goodall et al., 2009; Weavil et al., 2015) exhibit a peak in evoked response size followed by a decline at contraction strengths ≥ 50-75% of maximal voluntary contraction (MVC) during isometric conditions. However, the triceps brachii (Todd et al., 2003) and some lower limb muscles, such as the soleus, exhibit a continuous increase in MEP size with force output (Oya, Hoffman, & Cresswell, 2008), consistent with the relationship between motor unit recruitment and firing rates in a muscle.

The motor unit strategy of a muscle might not be the only factor determining the corticospinal output with increases in nervous system gain. For example, corticospinal excitability has been

shown to be reduced during maximal (Doguet et al., 2017; Julien Duclay, Pasquet, Martin, & Duchateau, 2011) and submaximal (Abbruzzese, Morena, Spadavecchia, & Schieppati, 1994; J. Duclay, Pasquet, Martin, & Duchateau, 2014; Gruber, Linnamo, Strojnik, Rantalainen, & Avela, 2009) lengthening compared to shortening and/or isometric contractions at a similar relative torque output. Some researchers have made inferences that the corticospinal behaviour might be similar during shortening and lengthening contractions with increases in torque output (J. Duclay et al., 2014), but these investigations have been limited in the number of contraction intensities studied. Thus, it remains contentious whether a similar trend of the contraction intensity–MEP response curve is observed during the two types of anisometric contraction. Therefore, the purpose of this study was to assess the effect of contraction intensity during shortening and lengthening contractions on the modulation of MEP amplitude. Only submaximal intensities up to 80% MVC were studied since they have a greater relevance to the activities of daily living and in order not to confound the corticospinal behaviour in the present study with potential fatigue. We hypothesised that MEPs would be lower during lengthening compared to shortening contractions, but, based on previous work in the soleus, the contraction intensity-MEP curves would exhibit similar profiles during both contractions types. The tibialis anterior (TA) was chosen as the muscle of interest due to its unique characteristics. Specifically, dorsiflexors have been shown to exhibit greater torque producing capacity during lengthening compared to shortening contraction (Pasquet *et al.*, 2000; Reeves & Narici, 2003; Klass *et al.*, 2007; Duchateau & Enoka, 2016), which might not be the case for all human muscles (Duchateau & Enoka, 2016). Furthermore, due to its role in locomotion (Byrne, O'Keeffe, Donnelly, & Lyons, 2007) and the need for accuracy of toe clearance (Capaday, Lavoie, Barbeau, Schneider, & Bonnard, 1999), the TA exhibits a facilitated corticospinal response during human walking (Capaday et al., 1999; Schubert,

Curt, Jensen, & Dietz, 1997) highlighting the functional need to investigate the corticospinal behaviour of this specific muscle.

METHODS

Ethical approval

The procedures of this study were approved by Northumbria University Faculty of Health & Life Sciences Ethics Committee (RE070112538) in accordance with Declaration of Helsinki with the exception of registration in a database.

Participants

Thirty healthy, young individuals (including 6 females; 25 ± 4 yrs; 175 ± 10 cm, 76.1 ± 9.9 kg) provided written informed consent to take part in the study. Participants were both from resistance-trained (n = 4) and untrained population since previous work has shown no effect of resistance-training status on MEP amplitude in the TA (Tallent, Goodall, Hortobágyi, St Clair Gibson, & Howatson, 2013). A mixed-sex sample was studied to be able to extrapolate the findings to a wider population. However, as highlighted recently (Sims & Heather, 2018), controlling for changes in hormonal milieu is necessary for human physiological studies including both sexes. To reduce the potential influence of female sex hormones on neuronal function (Smith, Adams, Schmidt, Rubinow, & Wassermann, 2002), all females were tested in the early follicular phase of the menstrual cycle where the quantities of both oestrogen and progesterone are likely to be low (Elliott, Cable, Reilly, & Diver, 2003). The start of the early follicular phase was defined as the onset of menstruation and participants were tested within 3 days of that. All participants were free of cardiorespiratory, neurological, neuromuscular

disorders or lower body musculoskeletal injury. They also reported no contraindications to transcranial magnetic stimulation (TMS) and were not taking any medication known to affect the nervous system. Participants refrained from caffeine and strenuous exercise for 6 and 48 hours prior to the experimental session, respectively.

Study design

Participants visited the laboratory twice, first for familiarisation followed by the experimental session 48-72 hours after. The familiarisation session included habituation with stimulation techniques and practice of the torque-matching task during different contraction types and intensities as per the experimental protocol which was performed in its entirety. During the experimental session, participants had MEPs elicited during shortening and lengthening contractions in the TA across a range of contraction intensities (15, 25, 50 and 80% of contraction type specific MVC). The order of contraction type and intensity were randomised. Eight trials were performed per contraction type and intensity and those responses were averaged and used for data analysis. The experimental protocol is depicted in Figure 1.

Procedures

Experimental setup

Participants were sat in an isokinetic dynamometer (Cybex Norm, NY, USA) with the foot of the dominant limb strapped firmly on the motor plate of the device with the knee and hip kept at 120° (180º = full extension) and 90°, respectively. Contractions were performed by assisting or resisting the power head of the device during shortening and lengthening actions, respectively, as the ankle moved through a 30° range of motion (75° to 105°) at an angular

velocity of 15°·s^{-1}. All stimuli were applied as the ankle passed through anatomical zero (90°). Prior to eliciting MEPs during shortening and lengthening dorsiflexion, a specific contraction type MVC was performed (Škarabot et al., 2018), with the MVC torque value recorded at anatomical zero.

Electromyography

Surface electromyography (EMG) was recorded using bipolar EMG electrodes (8 mm diameter, 20 mm inter-electrode distance; Kendall 1041PTS, Tyco Healthcare Group, MA, USA) placed on the belly of TA at one-third of the length between the head of the fibula and the medial malleolus with the reference electrode on the medial malleolus according to SENIAM recommendations (Hermens, Freriks, Disselhorst-Klug, & Rau, 2000). Prior to placement of electrodes, the recording site was shaved, abraded with preparation gel and wiped clean with an alcohol swab to ensure appropriate impedance (< 2 kΩ). The EMG signal was amplified (×1000), band pass filtered (10-1000 Hz; D360, Digitimer, Hertfordshire, UK) and sampled at 5 kHz (CED Power 1401, Cambridge Electronic Design, UK).

Transcranial magnetic stimulation

A magnetic stimulator (Magstim 200^2, Magstim Ltd., UK; maximal output of ~1.4 T) with a posterior-to-anterior current, 110 mm double-cone coil was used to evoke MEPs in TA of the dominant leg. Initially, the coil was positioned over the reported optimal spot for stimulation of the TA muscle, roughly 0.5-1 cm lateral and posterior to the vertex (Devanne, Lavoie, & Capaday, 1997), after which the coil was moved around the initial spot in small steps until the position evoking the biggest potential in TA (hotspot) was found. After that, resting motor

threshold (RMT) was determined, defined as a stimulus intensity that evoked peak-to-peak MEP amplitude ≥ 50 μV in 5 out of 10 trials (Rossini et al., 2015). During the experiment, the pulses were delivered at 1.2 × RMT as it lies on the middle portion of the ascending part of the stimulus-response curve (Han, Kim, & Lim, 2001) and is thus sensitive to changes in corticospinal excitability. All contractions were separated at least 30 seconds to ensure MEPs had returned to resting values (Tallent et al., 2012).

Percutaneous nerve stimulation

The maximal muscle response (M_{max}) was elicited with a 40 mm diameter cathode/anode arrangement over the peroneal nerve (1 ms pulse duration; Digitimer DS7AH, Welwyn Garden City, Hertfordshire, UK). Once optimal electrode location had been identified, it was marked with a permanent marker and the electrode was strapped to participant's leg. The current of the stimulation was increased until no further increase in the evoked response during rest was observed, after which the current was additionally increased by 50% to ensure supramaximal intensity of stimulation. To account for possibility of M_{max} modulation with contraction type and intensity (Lee & Carroll, 2005), M_{max} was then elicited during specific muscle action (shortening and lengthening) and intensity (15, 25, 50 and 80% of contraction type specific MVC) and later used to normalise responses to TMS.

Data analysis

All data were recorded in a 500 ms window including 50 ms before TMS was delivered (Signal v3, CED, UK). Background EMG activity was assessed as the mean rectified EMG activity obtained 25 ms prior to the stimulus and was normalised to peak-to-peak amplitude of

198 M_{max} (EMG/M_{max}; Lanza *et al.*, 2018). Peak-to-peak amplitude of MEP was calculated and
199 expressed relative to the amplitude of M_{max} (MEP/M_{max}).

200

201 **Statistical analysis**

202 A 2 × 4 ANOVA (2 – contraction type, 4 – contraction intensity) was performed to assess the
203 effect of contraction type and intensity on EMG/M_{max} and MEP/M_{max} (SPSS Inc., Chicago,
204 IL, USA). Post hoc analyses were performed using pairwise comparison with Bonferroni
205 correction. Significance was accepted at an alpha level of 0.05. All data are presented as
206 means ± standard deviation (SD).

207

208 **RESULTS**

209 EMG/M_{max} increased with contraction intensity ($F_{1.2,\ 33.4} = 101.8$, $p < 0.001$, $\eta_p^2 = 0.78$) in a
210 progressive manner ($p < 0.001$ for all; Figure 2A), but was similar between contraction types
211 ($F_{1,\ 29} = 2.0$, $p = 0.171$, $\eta_p^2 = 0.06$). However, MEP/M_{max} was greater during shortening
212 compared to lengthening contractions ($F_{1,\ 29} = 13.6$, $p = 0.001$, $\eta_p^2 = 0.32$), but also increased
213 with contraction intensity ($F_{1.6,\ 46.6} = 86.6$, $p < 0.001$, $\eta_p^2 = 0.75$) in a step-wise manner ($p <$
214 0.001 for all; Figure 2B) during both contraction types.

215 The continual increase in corticospinal excitability across contraction intensities is also shown
216 in a representative example (Figure 3). MEP/M_{max} ratio in this participant increased from 0.38
217 to 0.42, 0.46 and 0.56 during shortening and from 0.30 to 0.38, 0.40 and 0.50 during
218 lengthening contractions at 15, 25, 50 and 80% MVC. The behaviour was similar across all
219 participants (Figure 4).

DISCUSSION

The present data showed an increase in the size of the MEP amplitude with incremental torque output up to 80% of maximal torque regardless of contraction type. This is the first study to have explored the behaviour of corticospinal excitability with varying nervous system gain and corroborates the experiments using isometric experimental models on other lower leg muscles such as gastrocnemius and soleus where continual increase in corticospinal and spinal excitability was observed with increments in torque output (Oya et al., 2008). This has been related to the motor unit recruitment being the primary strategy for incremental force control in plantarflexors (Grillner & Udo, 1971). However, the opposite is seen in muscles such as brachioradialis where increases in firing rate largely contribute to increments in force production at forces ≥ 75% MVC, resulting in a decrease in corticospinal excitability at high contraction strengths (Martin et al., 2006). Specifically, this decrease in corticospinal excitability has been related to unresponsiveness of the motoneuron pool to an external stimulus, which is likely due to refractory motoneurons as part of the after-hyperpolarisation of an action potential (Martin et al., 2006). As evidenced by animal work (Baldissera & Gustafsson, 1974; Schwindt & Calvin, 1972) and modelling studies (Jones & Bawa, 1999; Matthews, 1999), motoneurons exhibit an exponential return to threshold when firing rates are lower, whereas a more progressive return is evident with a greater discharge rate. Data from single motor unit recordings suggests that during non-ballistic contractions the TA exhibits a progressive recruitment of motor units up to ~90% MVC (Desmedt & Godaux, 1977; Van Cutsem, Duchateau, & Hainaut, 1998). Thus, given motor unit recruitment is the primary strategy of the TA for increasing force output, the graded increase in corticospinal excitability across contraction intensities in the present study supports the notion that the behaviour of evoked potentials is related to the motor unit strategy of a muscle.

Another factor that can affect the behaviour of corticospinal excitability with variations in torque output is the TMS stimulus intensity. It has been shown in upper limb muscles, with lower a stimulus intensity, a peak in MEP, followed by a MEP decline, occurs at a greater percentage of MVC compared to higher stimulus intensities (Martin et al., 2006). However, in lower limb muscles with smaller firing frequency of motor units, the decline in MEP at higher contraction intensity was not observed with higher stimulus intensity; rather the responses only plateaued (Oya et al., 2008). We did not examine the responses at intensities corresponding to maximal MEP amplitude and thus this question could be an avenue worth exploring in future investigations since it remains possible that different results would be obtained in the present study had greater TMS stimulus intensity been used. Furthermore, it has been suggested that the weaker projections to lower limb muscles might be responsible for the continual increase in corticospinal excitability with increased contraction strengths (Oya et al., 2008). However, the present data in the TA, a muscle which has a preferential input from the pyramidal tract into the spinal networks (Brooks & Stoney, 1971), and similar strength of corticomotoneuronal projections to the upper limbs (Brouwer & Ashby, 1990), suggest this is not the case. Therefore, it appears that motor unit control is still the primary factor determining a corticospinal response as the contraction intensity increases.

The continual increase of corticospinal output was observed during both shortening and lengthening contractions, despite a reduced corticospinal excitability during lengthening relative to shortening contractions, in line with other muscles of the upper and lower limbs (J. Duclay et al., 2014; Gruber et al., 2009). A previous study has shown a continual increase in corticospinal excitability from submaximal to maximal contraction strength in the soleus (J. Duclay et al., 2014), but the study was limited in the contraction strengths studied (only 50% and 100% MVC). Accordingly, the present study extends this observation of corticospinal excitability modulation with variations in torque output regardless of contraction type, across

differing submaximal intensities. Unlike the soleus, the difference in corticospinal output between shortening and lengthening contractions in medial gastrocnemius during submaximal contractions was absent during an MVC (J. Duclay et al., 2014). Since the present study did not investigate corticospinal excitability during maximal shortening and lengthening actions due to their lack of relevance in functional activities of daily living, it remains unknown whether similar behaviour is evident in TA. Thus, it is important to consider the responses observed in the present study in the context of the muscle and contraction intensities investigated. Whilst maximal contraction intensities are rarely going to be relevant for activities of daily living, inclusion of responses to TMS during maximal contractions, that represent the limit of torque producing capacity of an individual, and muscles with different motor unit recruitment strategies (e.g. the TA versus a hand muscle) would provide a more complete picture of corticospinal behaviour during different muscle actions with incremental torque output and might be something worth exploring in future studies. Given the reported motor unit control strategy of the TA with incremental torque output, it could be hypothesised that the evoked responses would peak at ~90% MVC (Desmedt & Godaux, 1977; Van Cutsem et al., 1998).

In conclusion, the contraction type–response curve of MEPs is similar during shortening and lengthening contractions when normalised to a contraction specific MVC. Despite differences in neural control of shortening and lengthening contractions, it appears that the relationship between motor unit recruitment and firing rate is the main mechanism determining corticospinal output with variations in nervous system gain.

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Competing interests

The authors have no competing interests to declare, financial or otherwise.

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Author Contributions

Experiments were performed in the Biomechanics Laboratory at Northumbria University. JŠ, JT, SG and GH designed the study protocol; JT acquired the data; JŠ, JT, SG, RD and GH analysed and interpreted the data; JŠ, JT, SG, RD and GH drafted or revised the final manuscript. All authors approved the final version of the manuscript and agree to be accountable for all aspects of the work. All persons listed qualify for authorship.

Figure captions

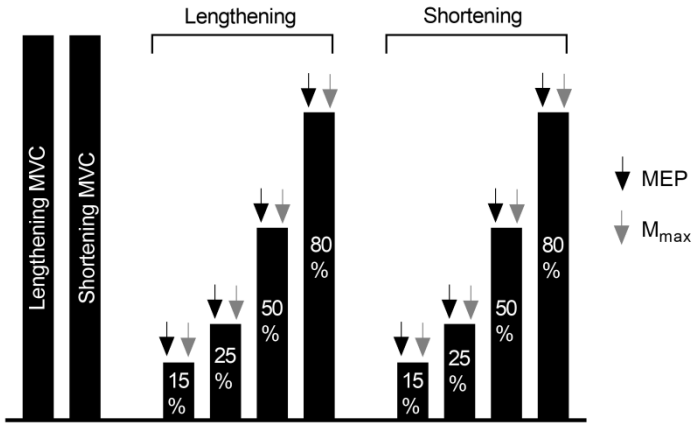
Figure 1. The experimental protocol. Participants first performed maximal shortening and lengthening contractions (MVC; randomised order) which was subsequently used for calculation of submaximal contraction intensities. Thereafter, participants performed shortening and lengthening contractions at 15, 25, 50 and 80% of contraction type specific MVC (pseudorandomised order) whilst receiving transcranial magnetic stimulation (black downward arrow) and percutaneous stimulation over the peroneal nerve (grey downward arrow) to elicit motor evoked potentials (MEP) and maximal compound action potentials (M_{max}), respectively. Participants performed the same protocol 2-3 days prior to the experimental session for the purposes of familiarisation.

Figure 2. Grouped data (mean ± SD) for background EMG activity (EMG/M_{max}; A) and motor evoked potentials normalised to maximal muscle response (MEP/M_{max}; B) during shortening and lengthening contractions at 15, 25, 50 and 80% of contraction-type specific maximal torque. $^{*}p < 0.005$ relative to lengthening, $^{\#}p < 0.001$ relative to other contraction strengths.

Figure 3. A representative example of motor evoked potentials across contraction intensities (15, 25, 50 and 80% MVC torque) during shortening (A) and lengthening (B) contractions from an individual that best represents the sample mean. Responses are shown from 50 ms before to 250 ms after the stimulus (as denoted by the vertical line representing the stimulus artefact). Each trace is an average of 8 waveforms.

Figure 4. Individual data for motor evoked potentials in tibialis anterior normalised to maximal muscle response during shortening and lengthening contractions at 15, 25, 50 and 80% of contraction-type specific maximal torque.

473 Figure 1



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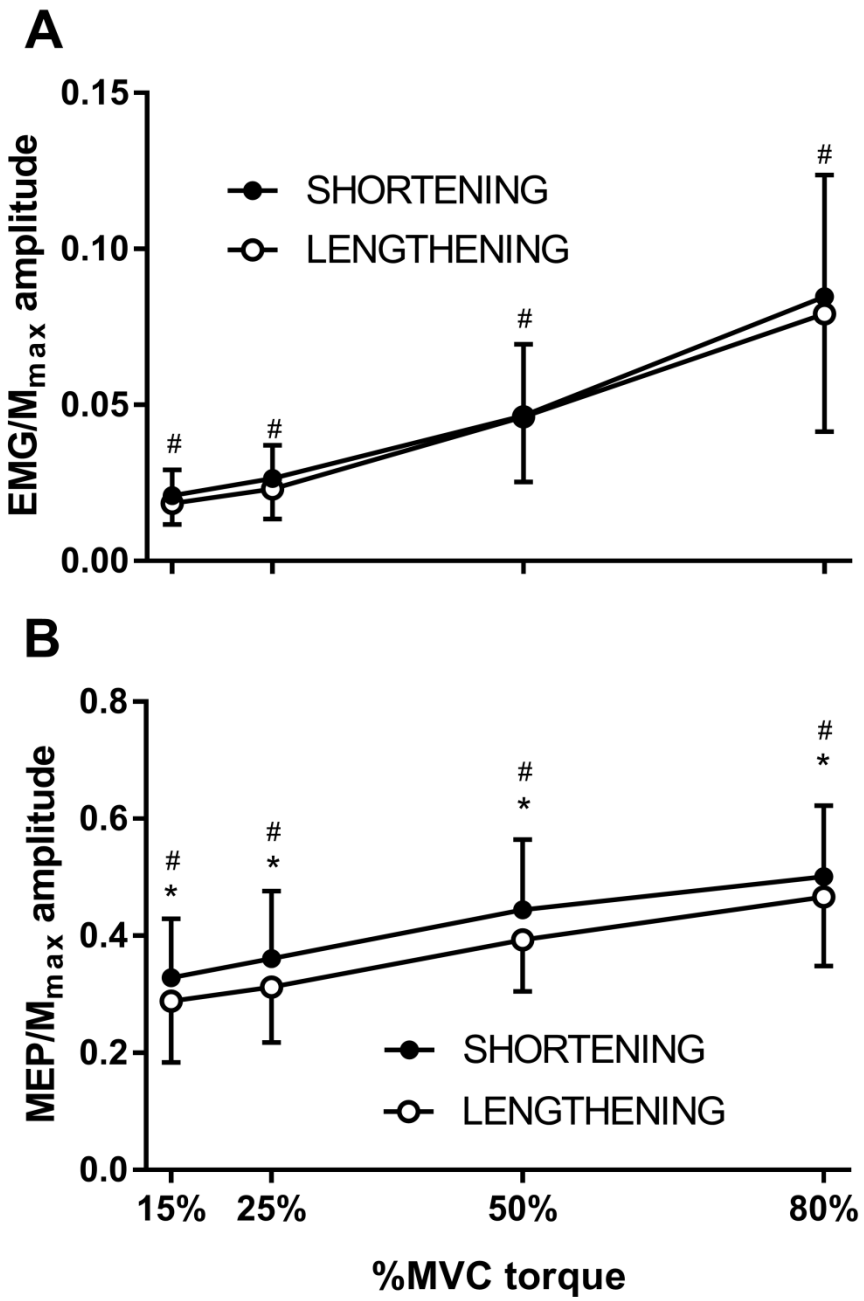
476 Figure 2



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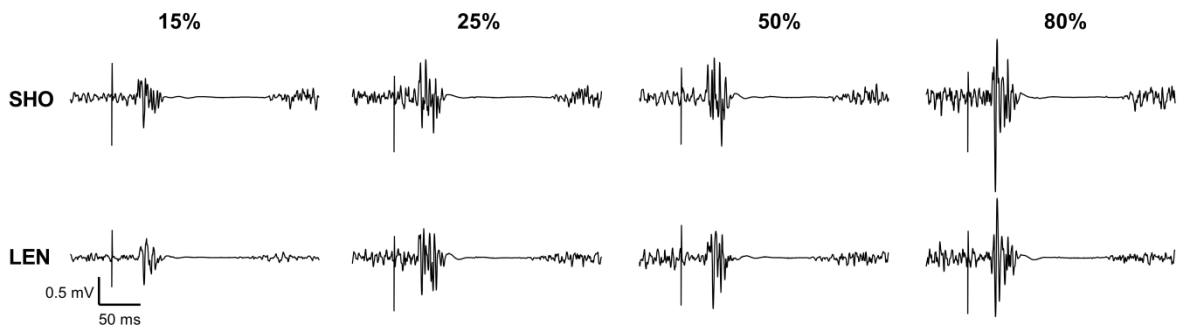
479 Figure 3



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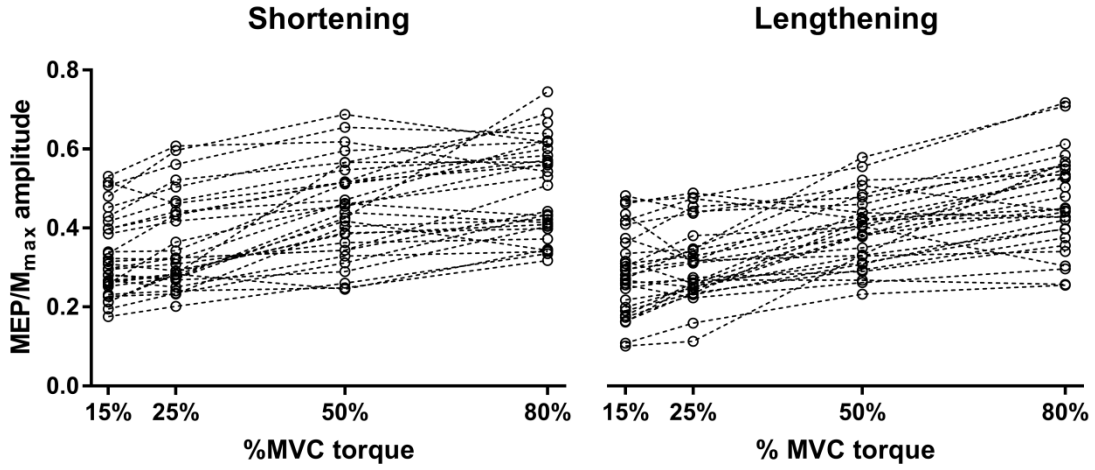
482 Figure 4



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